Guidance for Industry

Developing Medical Imaging Drugs and Biologics

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY[1]

Developing Medical Imaging Drugs and Biologics

I. INTRODUCTION

This guidance is intended to assist developers of medical imaging drug and biological products in planning and coordinating their clinical investigations and preparing and submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), abbreviated NDAs (ANDAs), and supplements to NDAs or BLAs.

Medical imaging drugs are generally governed by the same regulations as other drug and biological products.[2] However, as described in this document, many medical imaging drugs have special characteristics that can help guide developmental efforts. This guidance discusses some of these special characteristics and how drug development for medical imaging drugs can be tailored to reflect those characteristics. Specifically, this guidance discusses the following items:

1. Potential claims for medical imaging drugs and the nature of promotional materials for such claims.[3]

2. Methods by which each of these claims may be established.

3. Special considerations in the clinical evaluation of efficacy.

4. Special considerations in the clinical evaluation of safety.

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[1] This guidance has been prepared by the Division of Medical Imaging and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research (CDER) and the Office of Therapeutics Research and Review in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on developing medical imaging drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] Sponsors developing medical imaging drugs should be familiar with Agency regulations and guidances pertaining to the development of drugs and biologics.

[3] The terms *claim*, *indication*, and *indication for use* are used interchangeably in this guidance.

In response to the requirements of the FDA Modernization Act of 1997, FDA recently proposed a rule to amend the drug and biologics regulations for one category of medical imaging drugs by adding provisions for the evaluation and approval of in vivo radiopharmaceuticals used in the diagnosis or monitoring of diseases (63 FR 28301, May 22, 1998). This guidance elaborates on the concepts contained in the proposed rule on radiopharmaceutical diagnostic products. Once the proposal is finalized, the Agency will revise this guidance, if necessary, to ensure that it is consistent with the final rule.

II. SCOPE: TYPES OF MEDICAL IMAGING DRUGS

This guidance applies to medical imaging drugs that are used for diagnosis or monitoring and that are administered in vivo. These include medical imaging drugs used with medical imaging techniques such as radiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and radionuclide imaging. The guidance is not intended to apply to the development of therapeutic uses or to in vitro diagnostic uses of these drugs.

Medical imaging drugs can be classified into two general categories:

A. Contrast Drug Products

Contrast drug products are used to increase the relative difference of signal intensities in adjacent parts of the body and to provide additional information in combination with an imaging device beyond that obtained by the device alone. These products include, but are not limited to, the following: (1) iodinated compounds used in radiography and CT; (2) paramagnetic metallic ions (such as ions of gadolinium, iron, and manganese) linked to a variety of molecules and used in MRI; and (3) microbubbles, microaerosomes, and related microparticles used in diagnostic ultrasonography.

B. Diagnostic Radiopharmaceuticals[4]

[4] As defined in the proposed rule for diagnostic radiopharmaceuticals, and as used in this guidance, a *diagnostic radiopharmaceutical* is (a) an article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons or (b) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such an article. The FDA interprets this definition to include articles that exhibit spontaneous disintegration leading to the reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons (63 FR 28301 at 28303).

Diagnostic radiopharmaceuticals are radioactive drugs that contain a radioactive nuclide that may be linked to a ligand or carrier.[5] These products are used in planar imaging, single photon emission computed tomography (SPECT), positron emission tomography (PET), or with other radiation detection probes.

Diagnostic radiopharmaceuticals used for imaging typically have two distinct components:

1. A radionuclide that can be detected in vivo (e.g., technetium-99m, iodine-123, indium-111). The radionuclide typically is a radioactive molecule with a relatively short physical half-life that emits radioactive decay photons having sufficient energy to penetrate the tissue mass of the patient. These photons may then be detected with imaging devices or other detectors.

2. A nonradioactive component that delivers the molecule to specific areas within the body. This nonradionuclidic portion of the diagnostic radiopharmaceutical often is an organic molecule such as a carbohydrate, lipid, nucleic acid, peptide, small protein, or antibody. In general, the purpose of the nonradioactive component is to direct the radionuclide to a specific body location or process.

III. INDICATIONS FOR MEDICAL IMAGING DRUGS

Because medical imaging drugs are used clinically in many diverse ways, this guidance outlines certain types of potential claims for these drugs. For example, some medical imaging drugs are not intended to provide disease-specific information, as characterized by measures such as sensitivity and specificity, but are intended to characterize structural or functional manifestations common to several diseases. In such cases, the proposed indications for these products may refer to structural or functional assessments that are common to multiple diseases or conditions.

Indications for medical imaging drugs may fall within the following general categories:

- Structure delineation
- Functional, physiological, or biochemical assessment
- Disease or pathology detection or assessment
- Diagnostic or therapeutic patient management

[5] In this guidance, the terms *ligand* and *carrier* refer to the entire nonradionuclidic portion of the diagnostic radiopharmaceutical.

These claims need not be mutually exclusive, and approval may be possible for claims other than those listed. Each of these claims is described in the following sections as is the nature of promotional materials for each of these claims. Ways in which each of these claims may be established are described in Section IV.

A. Structure Delineation

As described in the following sections, two types of claims for structure delineation may be possible: (1) locating and outlining normal anatomic structures and (2) distinguishing between normal and abnormal anatomy.

1. Locating and Outlining Normal Anatomic Structures

A medical imaging drug approved for this type of claim should be able to help locate and outline normal anatomic structures. The product also should help clarify the spatial relationship of the visualized normal structure(s) with respect to other body parts or structures.

Such a medical imaging drug may be developed to distinguish a normal structure that may not be seen well with other imaging drugs or modalities. For example, a contrast drug product may be developed to delineate the normal gastrointestinal tract to distinguish it from other abdominal structures or an abdominal mass. Similarly, a diagnostic radiopharmaceutical may be developed to image the normal parathyroid glands, which could help a surgeon plan and perform surgery for a mass in the thyroid gland. Products that help delineate normal anatomic variants also may be included here. An example of this type of product is a drug that delineates normal variants of coronary anatomy.

Promotional materials based on this claim may describe how the medical imaging drug enhances visualization of the normal anatomic structure, or its variants, and how it facilitates an understanding of the relationship of the normal visualized structure to other structures. However, promotional materials based on these claims should not imply that use of the product helps distinguish normal and abnormal anatomy, or that the product aids in the detection or assessment of disease or pathology. The materials should not imply that these products have been shown to facilitate appropriate diagnostic or therapeutic management decisions in patients. These types of uses fall within other claims.

2. Distinguishing Between Normal and Abnormal Anatomy

A medical imaging drug approved for this type of claim should be able to help locate and outline both normal and abnormal anatomic structures. The product also should help to clarify the spatial relationships of the normal and abnormal anatomic structure(s) with respect to other body parts or structures. This type of claim applies to situations where the mechanism by which the abnormal anatomy is visualized is sufficiently similar to the mechanism by which the normal anatomy is visualized. This type of claim does not apply to products whose mechanism of visualization is dependent on the presence of an abnormality.

Examples of this type of product include a medical imaging drug being developed to identify bronchiectasis. The drug might be able to distinguish dilated bronchi from normal bronchi and categorize the bronchiectasis anatomically (e.g., as cylindric, sacculated, or fusiform). Similarly, a medical imaging drug might be developed to evaluate meniscal or ligamentous injuries of the knee. Products that help delineate anomalous variants of normal anatomy may also be included here (e.g., a product that helps define the anatomical relationships of a vascular sling that compresses the trachea or esophagus).

Promotional materials based on such a claim may describe how the medical imaging drug helps distinguish between normal and abnormal anatomy or aids in identification of variants or anomalies of normal anatomy. Promotional materials based on these claims should not imply, beyond the description of the abnormal anatomy, that the product aids in the detection or assessment of disease or pathology. The materials should not imply that these products have been shown to facilitate appropriate diagnostic or therapeutic management decisions in patients.

A medical imaging drug that is intended either to (a) delineate nonanatomic structures such as tumors or abscesses or (b) detect disease or pathology within an anatomic structure should seek a claim of *disease or pathology detection or assessment or diagnostic* or *therapeutic patient management*, rather than this claim.

B. Functional, Physiological, or Biochemical Assessment

A medical imaging drug that is intended to provide functional, physiological, or biochemical assessment should be able to evaluate the function, physiology, or biochemistry of a tissue, organ system, or body region. Functional, physiological, and biochemical assessments are designed to determine if a measured parameter is normal or abnormal. This type of claim applies to drugs used to detect either a reduction or magnification of a normal functional, physiological, or biochemical process.

Examples of functional, physiological, or biochemical assessments include measurement of cardiac ejection fraction, assessment of regional cerebral blood flow, evaluation of myocardial wall motion, and assessment of anaerobic metabolites to evaluate tissue ischemia.

Promotional materials based on this type of claim may describe how the medical imaging drug facilitates assessments of function, physiology, or biochemistry. Promotional materials based on these claims should not imply that the use of these products aids in the detection or assessment of disease or pathology. The materials should not imply that these products have been shown to facilitate appropriate diagnostic or therapeutic management decisions in patients.

The claim of *functional, physiological, or biochemical assessment* is limited to assessment of normal functional, physiological, or biochemical processes when disturbances of these processes are common to several diseases or conditions and they are not diagnostic for any particular disease or condition. When these circumstances are not present, claims of *disease or pathology detection* or *assessment or diagnostic* or *therapeutic patient management* should be sought. For example, a claim of *disease or pathology detection or assessment* should be sought by sponsors who wish to develop a medical imaging drug to:

- Establish a diagnosis by detecting or assessing the function, physiology, or biochemistry of a tissue, organ system, or body region;

- Detect or assess an abnormality of function, physiology, or biochemistry that is diagnostic for a disease or condition;

- Detect or assess an abnormality of function, physiology, or biochemistry that is diagnostic for a specific disease or condition in the defined clinical setting for which the test will be indicated and used (see Section III.C);

- Detect or assess functional, physiological, or biochemical processes that are not expressed by the normal organ system, tissue, or body part.

C. Disease or Pathology Detection or Assessment

A medical imaging drug that is intended for disease or pathology detection or assessment should be able to assist in the detection, location, or characterization of a specific disease or pathological state in a defined clinical setting.[6]

[6] See Section IV.C for a definition of *defined clinical setting*.

Examples of medical imaging drugs for this type of indication include (1) a peptide that participates in an identifiable transporter function associated with a specific neurological disease; (2) a peptide that is specifically metabolized and is used to evaluate an abnormal cell's residual metabolic function in a particular disorder; and (3) a radiolabeled monoclonal antibody that attaches to a tumor antigen and thus detects a tumor.

Promotional materials based on this claim may describe how the medical imaging drug facilitates detection or assessment of a specific disease or pathology in the defined clinical setting in which it was studied. Promotional materials based on this claim should not imply that use of these products leads to particular changes in diagnostic or therapeutic patient management or in clinical outcomes.

D. Diagnostic or Therapeutic Patient Management

A medical imaging drug that is intended to assist in diagnostic or therapeutic patient management may be studied explicitly for its ability to provide imaging or related information leading directly to appropriate diagnostic or therapeutic management decisions in patients in a defined clinical setting. In this context, *explicitly* means that the hypotheses of how the medical imaging drug might be useful in diagnostic or therapeutic management should be specified in the protocol. Hypotheses should be tested prospectively in the clinical study and should be evaluated with endpoints that assess the appropriateness of patient management or clinical outcomes.[7] For example, a medical imaging drug may assist in appropriate determination of whether patients (1) should undergo diagnostic coronary angiography (i.e., the test results aid in a diagnostic management decision); (2) will have predictable clinical benefit from coronary revascularization (i.e., the test results aid in a therapeutic management decision); or (3) should undergo resection of a tumor or undergo chemotherapy (i.e., the test results aid in therapeutic management decisions). Labeling indications for these examples might include statements that a drug is indicated *to help determine the need for coronary angiography* or *to assist in the evaluation of tumor resectability.*

Promotional materials for this type of claim may describe how the medical imaging drug assists in diagnostic or therapeutic patient management.

E. Multiple Claims

The indication categories outlined above are flexible, and claims for medical imaging drugs need not be mutually exclusive. For example, a diagnostic radiopharmaceutical may be

[7] As used in this guidance, *clinical outcomes* refers to changes in patient symptoms, functioning, or survival.

developed as an aid in the diagnosis of lung cancer for a claim of *disease or pathology detection or assessment*. This diagnostic radiopharmaceutical could also be evaluated for its ability to provide information that leads directly to appropriate therapeutic management decisions (e.g., helping to determine, based on test results, what combination of surgery, radiotherapy, and chemotherapy might be appropriate).

Clinical studies should usually evaluate the effect of the imaging agent on both structure and function when both are commonly evaluated together in clinical practice (e.g., as during ultrasonography). For example, an ultrasound contrast drug used to assess stenotic blood vessels could be approved for both structural delineation and functional assessment if appropriate clinical studies were performed. In this case, clinical studies could be designed so that structural delineation of blood vessels is evaluated with two-dimensional ultrasonographic imaging. The functional assessment of the hemodynamic consequences of the obstructions could be evaluated with Doppler interrogation of the same vessels.

F. Other Claims

For a claim that does not fall within the indication categories identified above, the applicant or sponsor should consult FDA on the nature of the desired claim and how to establish effectiveness for it.

IV. ESTABLISHING CLAIMS FOR MEDICAL IMAGING AGENTS

To establish a claim for a medical imaging drug, a sponsor or applicant should characterize the drug's clinical usefulness and demonstrate that the information provided is valid and reliable.[8] Clinical studies should be performed in defined clinical settings. These overarching principles are discussed in this section, as are the methods of establishing effectiveness for specific claims.

A. Clinical Usefulness

The principal reason for performing an evaluation with a medical imaging drug is to determine that the diagnostic results will be useful to the patient and the health care provider. As is the case with therapeutic drugs, claims for medical imaging drugs should be supported with information demonstrating that the potential benefits of the use of a medical imaging drug outweigh the potential risks to the patient. Potential risks include

[8] As used in this guidance, *validity* is a global concept that encompasses the quality of bias. Valid measurements are close to the *truth* (have small bias). *Reliability* is a concept that encompasses the quality of precision. Reliable measurements are reproducible (have small variance).

both the risks related to administration of the drug and the risks of incorrect diagnostic information. Incorrect diagnostic information includes, but is not limited to, inaccurate structural, functional, physiological, or biochemical information; false positive or false negative diagnostic determinations; and information leading to inappropriate decisions in diagnostic or therapeutic management.

A medical imaging drug that is clinically useful provides information that contributes to the appropriateness of diagnostic or therapeutic patient management, contributes to beneficial clinical outcome, or provides accurate prognostic information.

In addition, for a contrast drug product to be considered clinically useful, the product used in combination with an imaging device should provide useful information beyond that obtained by the imaging device alone. Stated differently, imaging with the contrast drug product should add value when compared to imaging without the contrast drug product.

A plan for establishing clinical usefulness should be incorporated into the development plan of a medical imaging drug. In general, clinical usefulness should be evaluated prospectively in the principal clinical studies of efficacy (e.g., by incorporation into Phase 3 protocols).[9]

B. Validity of Information Provided by a Medical Imaging Drug

A medical imaging drug may be shown to provide valid information in at least two ways:

1. Comparing the results yielded by the medical imaging drug with those of a truth standard (*gold standard*).[10]

2. Demonstrating that the use of the product contributes to beneficial patient outcomes.

In instances where a truth standard does not exist or cannot be assessed practically, the focus of the study should be to evaluate the effects of the product on clinical outcomes. For example, clinical outcomes could be assessed in a study designed to evaluate the effects of the medical imaging drug on *diagnostic or therapeutic management* (see Section IV.D.4).

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[9] In some situations (e.g., measurement of cardiac ejection fraction), clinical usefulness may be documented by a critical and thorough analysis of the medical literature and any historical precedents.

[10] See Glossary and Section VIII.C.

C. Defined Clinical Settings

A *defined clinical setting* should reflect the circumstances and conditions under which the medical imaging drug is intended to be used. It delineates the patient population, relevant available medical and diagnostic data, and diagnostic questions that characterize the circumstances under which the medical imaging drug is intended to be used. For example, a medical imaging drug for duodenal ulcers could be developed for use in different defined clinical settings. The drug might be developed to identify or exclude duodenal ulcers in patients with gastrointestinal bleeding, to confirm a suspected duodenal ulcer in patients with equivocal findings on radiographic examination of the upper gastrointestinal tract, to evaluate healing of duodenal ulcers in patients after initial treatment, or to help determine whether patients with duodenal ulcers should undergo surgery or remain on maintenance medical therapy.

The circumstances and conditions under which the medical imaging drug is intended to be used should be evaluated in a clinical trial and may be described in the labeling using the following mechanisms.

1. Specifying aspects of the medical history and physical examination that are pertinent for determining the likelihood of the disease or condition that is in question. For example, a medical imaging drug intended to detect breast cancer might be evaluated for use in the assessment of (1) otherwise healthy women over 40 years of age, (2) women presenting with palpable breast masses, or (3) women with a family history of breast cancer.

2. Specifying a patient population that is at a particular step in the diagnostic sequence. For example, a diagnostic radiopharmaceutical may be intended to evaluate patients in an emergency room with equivocal clinical and laboratory findings of a myocardial infarction, or to evaluate the location and extent of a myocardial infarction in patients with definitive findings.

3. Specifying any other diagnostic assessments that are to be performed in the evaluation of this patient population. This delineation should include describing how the medical imaging drug should be used with respect to other diagnostic tests or evaluations, including (1) whether the medical imaging drug is intended to be used together with, or as a replacement for, other diagnostic tests or modalities, and (2) how the use of the medical imaging drug is influenced by the results of other diagnostic evaluations. For example, in the evaluation of suspected pulmonary embolism, a medical imaging drug could be developed either as a replacement for ventilation-

perfusion scanning or as an adjunct to ventilation-perfusion scanning. If the medical imaging drug is developed to be an adjunct to ventilation-perfusion scanning, its intended use will likely be influenced by the scan results (e.g., intended for use in patients with scan results that are indeterminate and not for patients with *low-probability* or *high-probability* scans).

Clinical trials should prospectively evaluate relevant hypotheses about the demarcated patient population in the clinical setting in which the drug is intended to be used.

D. Establishing Effectiveness for Specific Claims

The following sections describe how each of the types of claims summarized in Section III may be established.

1. Structure Delineation

Methods by which claims for *structure delineation* may be established are described below.

a. Locating and Outlining Normal Anatomic Structures

A claim of *delineating normal anatomic structures* may be established by demonstrating in clinical studies that the medical imaging drug can reliably locate and outline normal anatomic structures and reliably clarify the spatial relationship of these structures to other body parts.

In clinical studies, the validity of the delineation should be demonstrated by comparing the performance of the medical imaging drug with that of a reference product or procedure of known high validity (i.e., a truth standard). Ideally, the high validity of this reference product or procedure should be thoroughly and critically documented before initiating the clinical efficacy studies.

In some cases, valid reference products or procedures may not be available or cannot be used. In these cases, the validity of the medical imaging drug may be demonstrated with clinical studies documenting that the product provides information that is consistent with known anatomic and structural facts about the tissue, organ, or body part in question. The sponsor should

discuss these anatomic and structural facts with the Agency and carefully detail and document them prior to initiation of the clinical efficacy studies.

b. Distinguishing Between Normal and Abnormal Anatomy

A claim for *distinguishing between normal and abnormal anatomy* may be established by demonstrating in clinical studies that the medical imaging drug can reliably locate and outline both normal and abnormal variations of an anatomic structure, and that the product is able to clarify the spatial relationships of the normal and abnormal anatomic structures with respect to other body parts or structures.

The validity of this distinction should be supported by studies in which sufficient numbers of subjects with and without abnormalities are appropriately represented. *Appropriate representation* means that the studies should generally include subjects that adequately represent the spectra of normality and abnormality (e.g., including subjects with chronic bronchitis, pneumonia, asthma, and cystic fibrosis; and also subjects with localized and diffuse disease for a drug intended to assess bronchiectasis) as well as the full range of disease severity (e.g., from mild to severe disease, or from early to advanced disease).

Appropriate preclinical studies in relevant animal models, if available, may provide additional information to support structure-delineation claims.

2. Functional, Physiological, or Biochemical Assessment

This type of claim may be established by demonstrating in clinical studies that the medical imaging drug can reliably measure a function or a physiological or biochemical process. These measurements should generally be validated by comparing the performance of the medical imaging drug with that of a reference product or procedure of known high validity (i.e., a truth standard). Ideally, the high validity of this reference product or procedure should be thoroughly and critically documented before its use in clinical studies.

These studies should provide a quantitative or qualitative understanding of how the measurement varies in normal and abnormal subjects or tissues, including the parameter's normal range, distribution, and confidence intervals in these subjects or tissues. When possible, the minimum detectable limits and reproducibility of the measurement should be assessed.

The parameter should be evaluated in sufficient numbers of both normal and abnormal patients. These patients should adequately represent the full spectra of normality and abnormality (e.g., including patients with inflammatory, neoplastic, and infectious intracranial processes for a drug intended to assess regional cerebral blood flow) and the full range of functional, physiological, or biochemical dysfunction (e.g., from minimal or no perfusion to luxury perfusion).

The drug's pharmacology in the setting of various functional, physiologic, or biochemical processes also should be documented from appropriate studies in relevant animal species, if available. These might include approaches such as induction of pharmacologic perturbations in the system to be evaluated (e.g., administration of a specific receptor antagonist that results in altered binding of the medical imaging drug); correlation with other accepted means of measuring particular parameters (e.g., evaluation of the cardiac ejection fraction by comparison to results obtained with radionuclide ventriculography); and in vivo or in vitro analyses (e.g., tissue autoradiography). Documentation should be obtained in at least one appropriate and relevant animal species, if available, in which the particular function, physiology, or biochemistry is sufficiently similar to that of humans. For example, for a medical imaging drug being developed to evaluate receptors within the central nervous system, full biochemical characterization of rodent brains by tissue autoradiography may be appropriate.

3. Disease or Pathology Detection or Assessment

A claim of *disease or pathology detection or assessment* may be established by demonstrating in a defined clinical setting that the medical imaging drug is able to identify or characterize the disease or pathology with sufficient validity and reliability. In this context, the term *validity* refers to the overall diagnostic performance of the product as measured by factors such as sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios. *Reliability* in this context means that the overall diagnostic performance of the product has precision. The phrase *sufficient validity and reliability* means validity and reliability that are good enough to indicate that the product could be useful in one or more defined clinical settings.

Data demonstrating validity and reliability should be obtained from patients in defined clinical settings reflecting the proposed indications. Patients may present for diagnostic evaluation of a specific disease or condition in various clinical settings. Even though these patients may have the same disease or condition, the clinical usefulness of the medical imaging drug and the likelihood that patients have

the disease or condition will likely be different in each clinical setting. Therefore, the medical imaging drug should be evaluated in representative settings for which use is proposed. In most disease or pathology detection or assessment indications, pooling of efficacy data across defined clinical settings would likely be of limited value, and the medical imaging drug should be separately evaluated in sufficient numbers of patients in one or more of such settings. A claim for disease or pathology detection or assessment may specify the defined clinical setting and specify that the medical imaging drug is to be used in conjunction with other tests.

4. Diagnostic or Therapeutic Patient Management

A claim of *diagnostic or therapeutic patient management* may be established in clinical studies by demonstrating that in a defined clinical setting the test is useful in guiding appropriate patient management. *Appropriate patient management* means that diagnostic or therapeutic management decisions are validated as being proper based on the correct diagnosis of the patient or on clinical outcomes. The correct diagnosis may be documented by comparison with valid assessments of actual clinical status (e.g., a histological diagnosis of malignancy), through patient follow-up, or by evaluation of clinical outcomes.

Medical imaging drugs may seek the claims *disease or pathology detection or assessment,* or *diagnostic or therapeutic management*, or both. A clarification of the distinction between these claims is appropriate. The claim *disease or pathology detection or assessment* can be obtained by demonstrating, in a defined clinical setting, sufficient validity and reliability of the medical imaging drug to imply clinical usefulness. The claim *diagnostic or therapeutic management* will likely be more difficult to establish, given the same defined clinical setting. Generally, it will require prospectively designed trials with the objective of evaluating a specific hypothesis of how the medical imaging drug might be useful in diagnostic or therapeutic patient management in a defined clinical setting. The trials might include randomization (whether to receive the medical imaging drug), with an endpoint measuring appropriateness of management (given the ultimate correct diagnosis) or clinical outcome. Alternatively, all patients may receive the study drug if it is possible to determine both what the management would have been had the medical imaging drug not been used, and what the management would be because of information provided by the medical imaging drug. The trials should demonstrate that management based on findings using the medical imaging drug is superior to management without use of the medical imaging drug. A *patient management* claim may specify that the medical imaging drug is to be used in conjunction with other tests to affect a patient management decision.

V. GENERAL CONSIDERATIONS FOR SAFETY ASSESSMENTS OF MEDICAL IMAGING DRUGS

The safety evaluation of a medical imaging agent is generally similar to those of other drugs and biologics. However, in many cases, the special characteristics of medical imaging drugs allow nonclinical and clinical safety assessments to be relatively efficient. The following sections discuss the special characteristics of a medical imaging drug that may lead to a more focused safety evaluation. These characteristics include its dose or mass, route of administration, frequency of use, and biological, physical, and effective half-lives.[11]

A. Dose or Mass

Medical imaging drugs may be administered at low mass doses. For example, the mass of a single dose of a diagnostic radiopharmaceutical may be relatively small because device technologies can typically detect small amounts of a radionuclide. When a medical imaging drug is administered at a mass dose that is at the low end of the dose-response curve for adverse events, dose-related adverse events are less likely to occur.

B. Route of Administration

Some medical imaging drugs are administered by routes that decrease the likelihood of systemic adverse events. For example, medical imaging drugs that are administered as contrast media for radiographic examination of the gastrointestinal tract (e.g., barium sulfate) may be administered orally, through an oral tube, or rectally. In patients with normal gastrointestinal tracts, many of these products are not absorbed. Accordingly, systemic adverse events are less likely to occur in these patients. Therefore, after a sponsor demonstrates that such a product is not absorbed systemically in the population proposed for use, the product may be able to undergo a more efficient safety evaluation that primarily assesses local organ system toxicity, toxicities that are predictable (e.g., volume effects, aspiration), and effects after intraperitoneal exposure (e.g., after gastrointestinal perforation). However, if the product will be used in patients with gastrointestinal pathologies that increase absorption, more complete nonclinical and clinical safety evaluations should be performed.

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[11] See also the proposed rule on developing diagnostic radiopharmaceuticals (63 FR 28301, May 22, 1998). When a medical imaging drug does not possess any special characteristics, complete standard drug safety assessments should be performed.

C. Frequency of Use

Many medical imaging drugs, including both contrast drug products and diagnostic radiopharmaceuticals, are administered relatively infrequently and in single doses. Accordingly, adverse events that are related to long-term use or to drug accumulation are less likely to occur with these drugs than with drugs that are administered chronically. Therefore, the nonclinical and clinical development programs for such products may generally omit long-term, or traditional, repeat-dose safety studies. However, in clinical settings where it is likely that the medical imaging drug will be administered repeatedly (e.g., to monitor disease progression), repeat-dose studies should be performed to assess safety and efficacy.

D. Biological, Physical, and Effective Half-Lives[12]

Diagnostic radiopharmaceuticals may use radionuclides with short physical half-lives or may be excreted rapidly. The biological, physical, and effective half-lives of diagnostic radiopharmaceuticals are incorporated into radiation dosimetry evaluations that require an understanding of the kinetics of the distribution and excretion of the radionuclide and its mode of decay. Biological, physical and effective half lives should be taken into account in planning appropriate safety and dosimetry evaluations of diagnostic radiopharmaceuticals (see Sections VI. and XI.C).

VI. NONCLINICAL SAFETY ASSESSMENTS

The special characteristics of medical imaging drugs described above may allow for a more efficient nonclinical safety program. The nonclinical development strategy for a drug should be based on sound scientific principles; the drug's unique chemistry (including, for example, those of its components, metabolites, and impurities); and the drug's intended use. Sponsors are encouraged to consult with the Agency before submission of an IND application and during drug development for recommendations and advice about the overall nonclinical development plan and proposed nonclinical protocols. In part, the number and types of nonclinical studies that should

[12] *Biological half-life* is the time needed for a human or animal to remove, by biological elimination, half of the amount of a substance that has been administered. *Effective half-life* is the time needed for a radionuclide in a human or animal to decrease its activity by half as a combined result of biological elimination and radioactive decay. *Physical half-life* is the time needed for half of the population of atoms of a particular radioactive substance to disintegrate to another nuclear form.

be conducted depend on the phase of the drug's development, what is known about the drug or its drug class, its proposed use, and the indicated patient population.

In the discussion that follows, a distinction is made between biological products and drug products. Existing specific guidance for biological products is referenced but not repeated here.

A. Nonclinical Safety Assessments for Biological Products

Many biological products raise relatively distinct nonclinical issues (e.g., immunogenicity and species restrictions). To ensure consistency with section 351 of the Public Health Service Act, the following documents should be reviewed for guidance on the preclinical evaluation of biological medical imaging agents:

- *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*, ICH, November 1997.

- *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*, February 27, 1997.

B. Nonclinical Safety Assessments for Non-Biological Products

The following sections describe ways in which nonclinical assessments of safety may be performed for non-biological contrast drug products and diagnostic radiopharmaceuticals.

1. Contrast drug products

Because of the characteristics of contrast drug products and the way they are used, nonclinical safety evaluations of such drug products may be made more efficient with the following modifications:

- Long-term, repeat-dose toxicity studies in animals usually can be eliminated.

- Long-term rodent carcinogenicity studies usually can be omitted.[13]

- Reproductive toxicology studies can often be limited to an evaluation of embryonic and fetal toxicities in rats and rabbits and to evaluations of

[13] Circumstances in which carcinogenicity testing may be recommended are summarized in the ICH guidance S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals, March 1, 1996.

reproductive organs in other short-term toxicity studies.[14] However, a justification should be provided for any studies of reproductive toxicology that are not performed and a formal request should be made to waive them.[15]

Additional safety considerations for contrast drug products may include the following: their large mass dose and volume (especially for iodinated contrast materials that are administered intravenously); osmolality effects; potential transmetalation of complexes of gadolinium, manganese, or iron (generally MRI drugs); potential effects of tissue or cellular accumulation on organ function (particularly if the drug is intended to image a diseased human organ system); and the chemical, physiological, and physical effects of ultrasound microbubble drugs (e.g., coalescence, aggregation, margination, and cavitation).

2. Diagnostic Radiopharmaceuticals

Because of the characteristics of diagnostic radiopharmaceuticals and the way they are used, nonclinical safety evaluations of these drugs may be made more efficient by the following modifications:

- Long-term, repeat-dose toxicity studies in animals typically may be eliminated.
- Long-term rodent carcinogenicity studies usually may be omitted.
- Reproductive toxicology studies may generally be waived when adequate scientific justification is provided.[16]
- Waivers for the performance of genotoxicity studies may be granted when scientifically justified.[17]

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[14] See *S5A Detection of Toxicity to Reproduction for Medicinal Products* (ICH), September, 22, 1994, and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (ICH), April 5, 1996.

[15] Waiver regulations for INDs are set forth at 21 CFR 312.10; those for NDAs appear at 21 CFR 314.90.

[16] See ICH *S5A* and ICH *S5B*.

[17] See *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (ICH), April 24, 1996, and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (ICH), November 21, 1997.

In reproductive toxicology and genotoxicity studies, components other than the radionuclide should be considered separately because they may be genotoxins or teratogens, causing effects that may exceed those of the radioactivity alone.

Special safety considerations for diagnostic radiopharmaceuticals may include verification of the mass dose of the radiolabeled moiety; assessment of the mass, toxic potency, and receptor interactions for any unlabeled moiety; evaluation of all components of the final formulation for toxicity potential (e.g., excipients, reducing drugs, stabilizers, anti-oxidants, chelators, impurities, residual solvents); and potential pharmacologic or physiologic effects due to molecules that bind with receptors or enzymes.

3. Timing of Nonclinical Studies Submitted to an IND Application

Appropriate timing of nonclinical studies should facilitate the timely conduct of clinical trials (including appropriate safety monitoring based upon findings in nonclinical studies) and should reduce the unnecessary use of animals and other resources.[18] The recommended timing of nonclinical studies for medical imaging drugs is summarized below.

a. Completed Before Phase 1:

- Safety pharmacology studies. Particular emphasis should be placed on human organ systems in which the medical imaging drug localizes and on organ systems that the product is intended to visualize, especially if the organ system has impaired function.

- Toxicokinetic and pharmacokinetic studies (see ICH guidances).

- Single-dose toxicity studies. *Expanded acute* single-dose toxicity studies are strongly recommended.[19] However, if short-term, repeated-dose toxicity studies have been completed, nonexpanded, single-dose toxicity studies may be sufficient.

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[18] See *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (ICH), November 25, 1997.

[19] See *Single Dose Acute Toxicity Testing for Pharmaceuticals*, August 1996.

- For medical imaging drugs that are administered intravenously: (1) local tolerance and irritancy studies, including evaluations of misadministration or extravasation, (2) blood compatibility studies, including evaluations of hemolytic effects, and (3) effects on protein flocculation.

- Radiation dosimetry, if applicable.

- In vitro genotoxicity studies (see Section VI.B.2 for diagnostic radiopharmaceuticals).

b. Completed Before Phase 2:

- Short-term, repeated-dose toxicity studies.

- Immunotoxicity studies.

- In vivo genotoxicity studies (see Section VI.B.2 for diagnostic radiopharmaceuticals).

c. Completed Before Phase 3:

Reproductive toxicity studies if needed (see Section VI.B.2 for diagnostic radiopharmaceuticals).

d. Completed No Later Than the End of Phase 3:

- Drug interaction studies.

- In vivo or in vitro studies that further investigate adverse effects seen in previous nonclinical studies.

VII. GENERAL CONSIDERATIONS IN THE CLINICAL EVALUATION OF MEDICAL IMAGING DRUGS

Many considerations in the overall clinical development of drugs are summarized in ICH and FDA guidance documents.[20] The principles described in these documents also apply to the development of medical imaging drugs. These general developmental considerations include, but are not limited to, the demonstration of safety and efficacy; the procurement of adequate dose-response, pharmacodynamic, and pharmacokinetic data to support licensing; and special issues such as consideration of drug metabolites, drug-drug interactions, and special populations.

These documents also discuss issues of trial design, conduct, analysis, and reporting of individual clinical studies. The principles described in these documents apply to individual clinical studies of medical imaging drugs. Relevant topics include, but are not limited to, study objectives, study design, selection of subjects, dosage evaluation, selection of control groups, numbers of subjects, response variables (i.e., endpoints or outcome measures), methods of minimizing or assessing bias (e.g., by randomization and blinding), and issues in statistical analysis.

However, the development of medical imaging drugs for diagnostic purposes may also raise issues somewhat different from those raised during the development of therapeutic drugs. These issues deserve special attention. The following sections discuss some issues that are particularly relevant to medical imaging drug development. Considering them during the product development process may increase the efficiency of the clinical development of these products.

A. Phase 1 Studies[21]

Phase 1 studies can include, but are not limited to, assessments of the safety of single, increasing doses of a drug and evaluations of human pharmacokinetics. Depending upon the drug and its potential toxicities, these trials may begin in healthy volunteers or in patients. Screening for potential human toxicities may include serial evaluations of clinical laboratory tests (e.g., hematology, clinical chemistry, urinalysis), other laboratory tests (e.g., electrocardiograms), and adverse events. Pharmacokinetic evaluations should address the absorption, distribution, metabolism, and excretion of all components of the drug formulation and any metabolites. Sponsors are encouraged to consult with the appropriate FDA review division on pharmacokinetic issues. Evaluation of a medical imaging drug that targets a specific metabolic process or receptor should include assessments of the drug's potential effects on directly related functions.

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[20] See ICH efficacy guidances available on the Internet at http://www.fda.gov/cder/guidance/index.htm, or http://www.fda.gov/cber/guidelines/index.htm.

[21] See also guidance for industry, *Content and Format of Investigational New Drug Applications (INDs) for Phase-1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*, November 1995.

For diagnostic radiopharmaceuticals, organ/tissue distribution data over time should be collected to optimize subsequent imaging protocols and calculate radiation dosimetry (see Section XI.C). Whenever possible, pharmacokinetics and pharmacodynamic evaluations should be made not only for the diagnostic radiopharmaceutical itself, but also for the radionuclide and for the carrier or ligand. The effects of large doses of the diagnostic radiopharmaceutical (including the carrier or ligand and other vial contents) should usually be assessed. This can be achieved, for example, by administering large doses of the medical imaging drug with low specific activity, by administering the contents of an entire vial of the medical imaging drug (assuming that this approximates a worst-case scenario in clinical practice), or both.

B. Phase 2 Studies

Goals of Phase 2 studies of medical imaging drugs can include, but are not limited to, refining the product's clinically useful dose range or dosage regimen (e.g., bolus administration or infusion), answering outstanding pharmacokinetic and pharmacodynamic questions, providing preliminary evidence of efficacy, expanding the safety database, optimizing techniques and timing of image acquisition, and evaluating other critical concepts or questions about the drug.

Dose considerations include the following: adjustment of the character or amount of active and inactive ingredients, amount of radioactivity, amount of nonradioactive ligand or carrier, specific activity, and use of different radionuclides. Methods used to determine the comparability, superiority, or inferiority of different doses or regimens should be discussed with the Agency. To the extent possible, the formulation that will be used for marketing should be used in Phase 2 studies. When a different formulation is used, bioequivalence and other bridging studies may help document the relevance of data collected with the original formulation.

Phase 2 trials should be designed to define the appropriate patient populations for Phase 3 trials. To gather preliminary evidence of efficacy, however, both subjects with known disease (or patients with known structural or functional abnormalities) and subjects known to be normal for these conditions may be included in clinical studies. Methods, endpoints, and items on the case report form (CRF) that will be used in critical Phase 3 trials should be tested and refined.

C. Phase 3 Studies

The goals of Phase 3 efficacy studies typically are to confirm the principal hypotheses developed in earlier studies, demonstrate the efficacy and continued safety of the drug, and

validate instructions for use and for imaging in the population for which the drug is intended. The design of Phase 3 studies (e.g., dosage, imaging techniques and times, patient population, and endpoints) should be based on the findings in Phase 2 trials. The to-be-marketed formulation should be used, or else bridging studies should be performed.

When multiple efficacy studies are performed, the studies may be of different designs.[22] To increase the extent to which the results can be generalized, the studies should be independent of one another and should use different investigators, clinical centers, and readers that perform the *blinded* image evaluations (see Section VIII.B).

VIII. SPECIAL CONSIDERATIONS IN THE CLINICAL EVALUATION OF EFFICACY

The following sections describe special considerations for the evaluation of efficacy in clinical trials for medical imaging drugs.

A. Selection of Subjects

The subjects included in critical Phase 3 clinical studies should be representative of the population in which the medical imaging drug is intended to be used.

1. For claims (a) *structure delineation*, or (b) *functional, physiological, or biochemical assessment*, adequate numbers of subjects should be enrolled. The full range of severity of the structural or functional abnormality (e.g., from mild to severe disease, from early to advanced disease) should be appropriately represented. This is to provide adequate estimates of the validity and reliability of the medical imaging drug over the full range of conditions for which it is intended to be used. The spectrum of other conditions, processes, or diseases (e.g., inflammation, neoplasm, infection, trauma) that may confound interpretation of the results for the disease or condition of interest also should be appropriately represented.

   Subject selection may be based on representative diseases that involve similar alterations in structure, function, physiology, or biochemistry if it appears that the results may be extrapolated to other unstudied disease states based on a known common process. Appropriate models should be selected on a case-by-case basis.

[22] See guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998.

Data to justify inclusion of a particular disease should be thoroughly documented, as should the data to support why the results obtained from the models can be extrapolated to other diseases.

Adequate numbers of normal or unaffected subjects should be enrolled during drug development in appropriately designed trials to establish the performance for the imaging drug in this population.

2. For claims (a) *disease or pathology detection or assessment*, or (b) *diagnostic or therapeutic patient management*, adequate numbers of subjects should be enrolled to demonstrate the validity and reliability of the information provided by the medical imaging drug. Because the validity and reliability of the medical imaging drug may vary depending on the characteristics of the patients and the clinical setting, the enrolled patients should be evaluated in defined clinical settings reflecting the proposed indications. For example, if a drug is to be used as a tool to aid in the diagnosis of patients *suspected* of having Alzheimer's disease, studies should not be limited to patients in which Alzheimer's disease is already *known* to be present or absent.

   The pretest odds and pretest probabilities of disease should be estimated for all subjects to aid subsequent clinical use of the medical imaging drug. Whenever possible, these odds and probabilities should be derived from prespecified criteria of disease (e.g., history, physical findings, results of other diagnostic evaluations) according to prespecified algorithms.

B. Image Evaluations

Because of the many ways that imaging data may be acquired, reconstructed, processed, stored, and displayed and because of the diversity of imaging modalities, the following sections use the term *images* in a general way. *Images* include, but are not limited to, films, likenesses or other renderings of the body, body parts, organ systems, body functions, or tissues. Because of this heterogeneity, the general recommendations delineated below for image evaluation in clinical trials may need to be customized to be applied to a specific medical imaging drug or imaging modality. For example, an *image* of the heart obtained with a diagnostic radiopharmaceutical or an ultrasound contrast agent may in some cases refer to a *set* of images acquired from different views of the heart (e.g., short-axis and long-axis views). Similarly, an *image* obtained with an MRI contrast agent may in some cases refer to a *set* of images acquired with different pulse sequences and interpulse delay times.

The specific ways that images will be acquired, reconstructed, processed, stored, displayed, and evaluated in clinical studies should be documented clearly in the study protocol. Special emphasis should be placed on the particulars of the blinded image evaluation. Study reports should reiterate much of this information and should highlight any differences from the protocol in the conduct of the study, including any changes in the execution of the blinded image evaluations.

1. Characteristics of the Readers

In studies that are intended to demonstrate efficacy of a medical imaging drug, evaluations of images should be performed by readers that are both *independent* and *blinded* (as defined below). Independent, blinded image evaluations may not be entirely representative of the conditions under which the test drug will ultimately be used clinically, but they compel the readers to rely on objective image features in their assessments of the effects of the drug. These independent, blinded image evaluations are intended to limit possible biases that could be introduced into the image evaluation by non-independent or unblinded readers.

Independent readers are those who have not otherwise participated in the Phase 3 studies (e.g., as investigators) and who are not otherwise affiliated with the sponsor or with institutions at which the studies were conducted.

Blinded readers are those who are unaware (1) of treatment identity (particularly in studies where images have been obtained with more than one treatment) and (2) of patient-specific clinical information or the study protocol. That is, in clinical studies of medical imaging drugs, blinded readers should be *blinded* in several ways, including ways that may not be encompassed by the usual definitions of the term in therapeutic clinical trials. First, blinded readers should be unaware of the identity of the treatment used to obtain a given image. This is the common meaning of blinding in therapeutic clinical trials.[23] For example, in a comparative study of two or more medical imaging drugs (or two or more doses or administration regimens), the blinded readers should not know about the identity of the drug (or dose or method of administration) used to obtain the particular image. For contrast agents, this also may include lack of knowledge about which images were obtained prior to drug administration and which were obtained after drug administration, although sometimes this may be apparent upon viewing the images.

[23] See *E8 General Considerations for Clinical Trials* (ICH), December 17, 1997, and *E9 Statistical Principles for Clinical Trials* (ICH), September 16, 1998.

Second, blinded readers also should be unaware or have limited awareness of patient-specific clinical information or of the study protocol. Anatomic orientation to the images should be minimal. This meaning of *blinding* differs from the common way the term is used in therapeutic clinical trials. However, blinding in this sense is a critical aspect of clinical trials of medical imaging agents. For example, blinded readers should generally not have knowledge of the patients' final diagnoses and may have limited or no knowledge of the results of other diagnostic tests that were performed on the patients, including the results of other imaging studies. In some cases, blinded readers should not be familiar with the inclusion and exclusion criteria for patient selection that were specified in the protocol.

At least two independent, blinded readers (and preferably three or more) are recommended for each study that is intended to demonstrate efficacy. This provides a better basis for subsequent generalization of the findings in the studies. All images obtained in the study (i.e., not just those determined to be evaluable) should be read by the readers, including images of test patients, control patients, and normal subjects. Each reader should read the images independently of the other blinded readers and independently of any on-site readings performed by the investigators. Consistency among readers should be measured quantitatively (e.g., with the kappa statistic). Consensus reads may be done after the readings are completed, but should not be performed for primary efficacy evaluation of the test drug. Readers may be trained in scoring procedures using sample images from Phase 1 and Phase 2 studies. Meanings of all endpoints should be clearly understood for consistency.

Sequential unblinding (i.e., providing more and more clinical information to the readers) might be used to provide incremental information under a variety of conditions that may occur in routine clinical practice (e.g., when no clinical information is available, when limited clinical information is available, and when a substantial amount of information is available). This may be used to determine when or how the test drug should be used in a diagnostic algorithm.

2. Presentation of the Images to the Readers

Images may be presented to the readers in several ways. As described below, this image evaluation should usually consist of randomized readings that are separate, combined, or both. *Randomization* of images refers to merging the images obtained in the study (to the fullest degree that is practical) and then presenting images in this merged set to the readers in a random sequence. For example, when the efficacy of several diagnostic radiopharmaceuticals are being compared (e.g., a

comparison of a test drug to an established drug), the readers should generally evaluate individual images from the merged set of images in a random sequence.:

a. Separate Image Evaluations

S*eparate* image evaluations should generally be performed by independent, blinded readers in the efficacy evaluation of a medical imaging drug. Such image evaluations may not be entirely representative of the conditions under which the test drug will ultimately be used clinically. However, these conditions compel the readers to evaluate each image on its own merits, without reference to any other image, and help to limit possible biases that could be introduced into the image evaluation by a nonrandomized or combined image evaluation.

Separating images refers to segregating the images (to the fullest degree that is practical) from other images that were obtained in the same patient at different times or under different conditions. These segregated images can then be presented to the readers in random sequence so that images are not viewed simultaneously. For example, when both unenhanced and enhanced images are obtained as part of a study of a contrast drug product, the images obtained before administration of the contrast drug product (i.e., the *unenhanced* images) should generally be mixed with the images obtained after administration of the drug (i.e., the *enhanced* images). Individual images in this intermixed set should then be read in random sequence so that the unenhanced and enhanced images are not viewed simultaneously. Alternatively, in some cases, the individual unenhanced images may be evaluated in a random order, followed by an evaluation of the individual enhanced images in a random order. In settings where the unenhanced image will not be used in clinical practice, images should be evaluated in a separate fashion, to show, for example, that the information from the enhanced image, alone, is clinically and statistically superior to the information from the unenhanced image, alone.

b. Combined Readings

Combined readings by independent, blinded readers may also be useful in evaluating the efficacy of a medical imaging drug because this type of evaluation often resembles the conditions under which the drug will be

used clinically.[24] *Combining* the images refers to simultaneous, or nearly simultaneous presentation to the reader of two or more images that were obtained at different times or under different conditions. Sets of combined images can then be presented to the readers in random sequence. For example, in studies of contrast drug products, both unenhanced and enhanced images may be obtained. The images, which were obtained at different times and under different conditions, may be viewed simultaneously by the reader. Similarly, for a diagnostic radiopharmaceutical, serial images may be obtained after drug administration to determine the optimal time for imaging. These images may be viewed in a combined fashion.

However, when this type of reading is performed, it is often advisable that an additional *separate* image evaluation be completed on at least one of the members of the combination. In this way, differences in the evaluations of the combined reading with those of the separate reading may be assessed. The combined images and the separate image may then be evaluated statistically with a paired comparison. For contrast drug products, these differences should demonstrate that the information from the combined images is clinically and statistically superior to information obtained from the unenhanced image alone. For example, if a combined image evaluation is performed in a two-dimensional study of blood vessels with a microbubble ultrasound contrast agent (e.g., evaluation of the unenhanced and enhanced images side by side or in close temporal proximity), another evaluation of the separate, unenhanced image of the blood vessel (i.e., images obtained with the device alone) may allow the microbubble effects on the image to be assessed.

These combined evaluations should be designed to minimize the likelihood that the readers will know (or be able to recall) their assessment of the separate image assessment (or vice versa). Thus, different pages in the CRF should be used for the combined and separate evaluations, and the combined and separate image evaluations should usually be performed at different times without reference to prior results.

When differences between the combined and separate images are to be assessed, the combined CRF and separate CRF should contain items or

[24] If a randomized, combined reading is the only evaluation that is done, labeling of the medical imaging drug (e.g., the INSTRUCTIONS FOR USE) should specify that combined evaluations should be performed in clinical practice.

questions that are identical in order to allow differences to be calculated. For example, on the separate CRF for a contrast drug product seeking a structural delineation claim, the readers may be asked to rate the clarity of border delineation of a structure on an ordinal scale (e.g., 0, 1, 2, 3, 4). The combined CRF should ask the same question and the difference in grades could be calculated. The purpose of this approach is to minimize potential biases that may arise if the CRF contains only questions or items that ask for relative judgments to be made. If desired, however, additional comparative questions and items may be added to the combined pages in the CRF. For example, the readers may be asked to rate the relative clarity of border delineation in the second image compared to the first (e.g., better, same, worse).

C. Truth Standards (*Gold Standards)*

A truth standard provides an independent way of evaluating the same variable being assessed by the investigational drug. A truth standard is known or believed to give the true state of a patient or true value of a measurement. Truth standards are used to demonstrate that the results obtained with the medical imaging drug are valid and reliable.

1. To minimize potential bias, determination of the true state of the subjects (e.g., diseased or nondiseased) with a truth standard should be performed without knowledge of the test results obtained with the medical imaging drug or test agent.

2. For contrast drug products, the results of the unenhanced images should generally not be incorporated in the truth standard. This is to decrease possible spurious correlations that may result from an imaging modality *agreeing with itself*. Stated differently, the truth standard should provide an assessment of disease status that is *independent* of the imaging modality for which the medical imaging drug is intended. For example, for a CT contrast agent intended to visualize abdominal masses, unenhanced abdominal CT images generally should not be included in the truth standard. However, components of the truth standard might include results from other imaging modalities (e.g., MRI, ultrasonography).

From a practical perspective, diagnostic standards are derived from procedures that are considered more definitive in approximating the truth than the test drug. For example, histopathology or long-term clinical outcomes may be acceptable diagnostic standards for determining whether a mass is malignant. Diagnostic

standards may not be error free, but for purposes of the clinical trial, they are regarded as definitive. The choice of the standard should be discussed with the Agency during design of the clinical trials to ensure that it is appropriate.

As noted in the proposed rule for diagnostic radiopharmaceuticals, a valid assessment of actual clinical status may be provided by a diagnostic standard or standards of demonstrated validity. In the absence of such diagnostic standards, the actual clinical status may in some cases be established in another manner, e.g., through patient follow-up. However, when a suitable diagnostic standard is unavailable or cannot be assessed practically, consideration should be given to changing the focus of the study to evaluate the effects of the product on clinical outcomes (see Section IV.D.4).

Truth standards may be other diagnostic tests (e.g., tissue biopsy to evaluate whether a mass is malignant) or appropriate combinations of other clinical data and diagnostic tests. For example, a definitive determination about whether a patient enrolled in a clinical trial experienced an acute myocardial infarction could be obtained by evaluating the combination of patient history (e.g., nature and location of pain), 12-lead electrocardiogram (e.g., Q waves or not), and serum levels of cardiac enzymes (e.g., creatine phosphokinase) according to a prespecified algorithm. Using these data, a panel of experts that is blinded to the medical imaging results yielded by the test agent could then make the definitive determination about the presence or absence of disease (i.e., an acute myocardial infarction).

D. Controls

As in other adequate and well-controlled clinical studies, clinical trials of medical imaging drugs may be controlled for different purposes and in a number of different ways. Before selecting the controls, discussions with the Agency are strongly recommended.

1. Comparison to Establish Performance in Relationship to a Drug or Modality Approved for a Similar Indication

In the event that the test drug is being developed as an advance over an approved drug or other diagnostic modality, a direct, concurrent comparison to the approved comparator should be performed. The comparison should include an evaluation of both the safety and the efficacy data for the comparator and the test drug. Information from both test and control images should be compared not only to one another but also to an independent truth standard. This will facilitate an

assessment of possible differences between the test drug and the comparator and will complete the assessment of diagnostic validity (e.g., sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios) between the two. Note that two medical imaging drugs could have similar values for sensitivity and specificity in the same set of patients, yet have poor agreement rates with each other. Similarly, two medical imaging drugs could have good agreement rates, yet both have poor sensitivity and specificity values.

When a medical imaging drug is being developed for an indication for which other drugs or diagnostic modalities have been approved, a direct, concurrent comparison to the approved drug or diagnostic modality is encouraged. However, prior approval of a drug for use in a particular indication does not necessarily mean that the results of a test with that drug may be used as a truth standard. Note that For example, if a medical imaging drug has been approved on the basis of sufficient concordance of findings with truth as determined by histopathology, assessment of the new drug should also usually include determination of truth by histopathology.

2. Placebos

Whether the use of a placebo is appropriate in the evaluation of a medical imaging drug depends upon the specific drug, proposed indication, and imaging modality. In some cases, the use of placebos may help minimize potential bias in the conduct of the study, and may facilitate unambiguous interpretation of efficacy or safety data. However, in some diagnostic studies (such as ultrasonography), products that are generally considered as placebos (e.g., water, saline, or the test drug vehicle) can have some diagnostic effects. These should be used as controls to demonstrate that the medical imaging drug has an effect above and beyond that of the vehicle.

E. Endpoints

In the evaluation of images, objective, quantifiable endpoints should be used whenever possible (e.g., signal-to-noise ratios, delineation, opacification; size of lesion, number of lesions, density of lesions). These endpoints may be complemented by other endpoints that ask the blinded readers to *interpret* the meaning of the objective image features (e.g., to make an assessment about whether a mass is malignant or benign). For example, data on a lesion's features may be complemented with additional assessments that demonstrate the impact of the drug on the physician’s diagnosis.

Imaging CRFs should be designed to capture imaging endpoints, including technical features of the images as well as the location of, and interpretation of, findings. Subjective interpretations of findings should be supported by objective quantitative or qualitative information derived from the images. Items on the CRF should be carefully constructed to gather information without introducing a bias that indicates the answer that is being sought.

The proposed labeled indication should be clearly derived from specific items in the CRF and from endpoints and hypotheses that have been prospectively stated in the protocol.

IX. ISSUES IN IMAGE ACQUISITION AND HANDLING

A. Image Acquisition

In studies that compare the effects of a test drug with another drug or imaging modality, images taken before study enrollment with the comparator drug or modality should not be used to determine whether a patient is enrolled in the study. These images also should not be part of the database used to determine test drug performance. Such baseline enrollment images have inherent selection bias because they are unblinded and based on referral and management preferences. All images used to determine the efficacy of the test drug and the comparator drug (or imaging modality) should be taken after study enrollment and within a time frame when the disease process is expected to be the same.

B. Image Handling Procedures

Ideally, all images should be evaluated by the blinded readers. In some cases where large numbers of images are obtained or where image tapes are obtained (e.g., cardiac echocardiography), sponsors have used image selection procedures. This is strongly discouraged because the selection of images can introduce the bias of the selector. In cases where preselection is thought to be needed, the sponsor is encouraged to clearly identify and discuss the selection procedures with the appropriate Agency division before their implementation.

X. STUDY ANALYSIS

Many imaging agent trials are designed to provide dichotomous or ordered categorical outcomes, and it is important that appropriate assumptions and statistical methods be applied in their analysis. Statistical tests for proportions and rates are commonly used for dichotomous

outcomes, and methods based on ranks are often applied to ordinal data. Additional analyses based on odds ratios can provide further insight. Study outcomes can often be stratified in a natural way, such as by center or other subgroup category, and the Mantel-Haenszel[25] procedures provide effective ways to examine both binomial and ordinal data. Exact methods of analysis, based on conditional inference, should be employed when necessary. The use of model-based methods should also be encouraged. These techniques include logistic regression models for binomial data and proportional odds models for ordinal data. Log-linear models can be used to evaluate nominal outcome variables.

Dichotomous outcomes in studies that compare images obtained after the test drug to images obtained before the test drug are often analyzed as matched pairs, where differences in treatment effects can be assessed by using methods for correlated binomial outcomes. These studies, however, may be problematic because they often do not employ blinding and randomization. For active- and placebo-control studies, including dose-response studies, crossover designs can often be used to gain efficiency. It is important that subjects are randomized to order of treatment. If subjects are not randomized to order of treatment, a crossover analysis applied to the images may still be informative. Study results from a crossover trial should always be analyzed with methods specifically designed for such trials.

Diagnostic validity can be assessed in a number of ways. With pre- and post-images, for example, each could be compared to the truth standard, and the sensitivity and specificity of the pre-image compared to that of the post-image. Two different active agents can be compared similarly. Diagnostic comparisons can also be made when there are more than two outcomes to the diagnostic test results. Common methods used to test for differences in diagnosis include the McNemar test and the Stuart Maxwell test.[26] In addition, confidence intervals for sensitivity, specificity, and other measures should be provided in the analyses. Receiver operating characteristic (ROC) analysis is another approach that can be used to evaluate diagnostic accuracy.

XI. CLINICAL SAFETY ASSESSMENTS[27]

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[25] For more on this topic, see Fleiss, Joseph, L., *Statistical Methods for Rates and Proportions*, 2nd ed., 1981, John Wiley and Sons, New York; and Woolson, Robert, *Statistical Methods for the Analysis of Biomedical Data*, 1987, John Wiley and Sons, New York.

[26] Ibid.

[27] See also guidance for industry and reviewers, *Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs, and Biologics*, March 18, 1998; and the final rule, "Expedited Safety Reporting Requirements for Human Drug and Biological Products," October, 7, 1997 (62 FR 52237).

Clinical safety assessments of both contrast drug products and diagnostic radiopharmaceuticals may be tailored based on their characteristics (e.g., dose, route of administration, frequency of use, and biological half-life), on the results of nonclinical safety assessments, and on the results of clinical pharmacokinetic/biopharmaceutics studies.

This guidance defines two categories of medical imaging drugs: Group 1 and Group 2. The extent of clinical safety monitoring and evaluation differs for these two categories. Medical imaging drugs classified as *Group 1 medical imaging drugs* may be able to undergo a more efficient clinical safety evaluation during development. *Group 2 medical imaging drugs* should undergo a complete clinical safety evaluation. Both Group 1 and 2 diagnostic radiopharmaceuticals should undergo complete radiation dosimetry assessments.[28] Preliminary categorization of medical imaging drugs into one of these two groups may be based on findings in nonclinical studies.

A. Group 1 Medical Imaging Drugs

Group 1 medical imaging drugs have been shown to be biologically inactive in nonclinical studies and to have undetectable levels of biological activity in human studies when administered at dosages that are similar to those intended for clinical use. Group 1 diagnostic radiopharmaceuticals are a subset of this group.[29, 30]

To be included in Group 1, a medical imaging drug should have the following:

1. An adequately documented margin of safety between nonclinical and clinical use. The no-observable-effect level (NOEL),[31] as appropriately adjusted in suitable

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[28] See Section XI.C.

[29] This classification conforms with the proposed rule for diagnostic radiopharmaceuticals, which states that diagnostic radiopharmaceuticals may be categorized based on defined characteristics related to their risk.

[30] Group 1 diagnostic radiopharmaceuticals may include radionuclides, ligands, and carriers that are known to be biologically inactive. This group may include radionuclides, ligands, and carriers used at radiation doses or mass dosages that are similar to, or less than, those used previously. This group also may include radionuclides, ligands, and carriers that have been documented not to produce adverse reactions.

[31] In this guidance, the *no-observable-effect level* is defined as the dosage level of a medical imaging drug at which no biological effects are observed. These biological effects include, but are not limited to, those that are biochemical, physiologic, pharmacologic, or structural. These biological effects do not necessarily have to be adverse or *toxic*. Adverse and toxic effects should be evaluated in the most susceptible species with the most sensitive assay. For purposes of this guidance, *localization* of a medical imaging drug in a target organ or target tissue (e.g., by binding to a

animal species, should be at least one thousand times greater than the maximal dose and dosage to be used in human studies. To establish this margin of safety the NOEL should be determined in each of the following nonclinical studies:

a. expanded-acute, single-dose toxicity studies
b. short-term, repeated-dose toxicity studies
c. safety pharmacology studies

Appropriately adjusted means that dosage comparisons between animals and humans are suitably modified for factors such as body size (e.g., body surface area) and otherwise adjusted for possible pharmacokinetic and toxicokinetic differences between animals and humans (e.g., differences in absorption for products that are administered orally).

2. Completed and fully documented Phase 1 clinical trial experience in appropriately designed trials that are consistent with the animal data. The medical imaging drug should not demonstrate any biological activity in human trials. The human pharmacokinetic trials also should provide data that allow adequate comparisons of exposure to be made between humans and the animal species used in the nonclinical studies.

Alternatively, to be included in Group 1, a medical imaging drug should have a history of sufficient clinical use or of previous clinical trial experience that adequately documents the following:

a. No clinically detectable allergic, immunologic, biochemical, physiologic, or pharmacologic responses at clinical doses or dosages; and

b. No known dose-related toxicological risk or adverse event profile at clinical doses or dosages.

For Group 1 medical imaging drugs, reduced safety monitoring in Phases 2 and 3 of drug development is justified. However, if toxicity is noted during clinical development, appropriate clinical safety monitoring should be performed.

B. Group 2 Medical Imaging Drugs

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tissue receptor) is by itself not considered to be a biological effect, unless it produces demonstrable perturbations.

Group 2 medical imaging drugs have been shown to be biologically active in animal studies or in human studies when administered at dosages that are similar to those intended for clinical use. Group 2 diagnostic radiopharmaceuticals are a subset of this group.[32]

Group 2 medical imaging drugs include the following:

1. Any medical imaging drug that does not meet the criteria for a Group 1 medical imaging drug;

2. All biological medical imaging drugs; [33, 34]

3. Any diagnostic radiopharmaceutical containing a radionuclide that undergoes alpha or beta decay.

For Group 2 medical imaging drugs, standard safety evaluations and monitoring should be performed in clinical trials.

C. Radiation Safety Assessment for All Diagnostic Radiopharmaceuticals[35]

Radiation safety assessments should be documented for both Group 1 and Group 2 diagnostic radiopharmaceuticals. The radiation safety assessment should establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. Such an evaluation should consider dosimetry to the total body, to specific organs or tissues, and, as appropriate, to target organs or target tissues. The radiation doses of diagnostic radiopharmaceuticals should be kept as low as reasonably achievable (ALARA). The maximum tolerated radiation dose need not be

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[32] Group 2 diagnostic radiopharmaceuticals may also include radionuclides and carriers that are known to be biologically active. This group includes radionuclides and carriers used at radiation doses or mass dosages that are higher than those used previously, including radionuclides and carriers that have been documented to produce adverse reactions.

[33] Biological medical imaging products, such as radiolabeled monoclonal antibodies or monoclonal antibody fragments, are classified within Group 2 because of their potential to elicit immunologic responses.

[34] See also the final rule, "Adverse Experience Reporting Requirements for Licensed Biological Products," October 27, 1994 (59 FR 54042).

[35] This section is based largely on the radiation dosimetry section of *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use.* February 27, 1997.

established. For diagnostic radiopharmaceuticals, estimates of the organ dosimetry should be performed in animals prior to the first Phase 1 study. Phase 1 studies of diagnostic radiopharmaceuticals should include studies that will obtain sufficient data for dosimetry calculations (21 CFR 312.23(a)(10)(ii)).

1. General Considerations

An IND sponsor should submit sufficient data from animal or human studies to allow a reasonable calculation of radiation absorbed dose to the whole body and to critical organs upon administration to a human subject (21 CFR 312.23(a)(10)(ii)). The following organs and tissues should be included in dosimetry estimates: (1) all target organs/tissues; (2) bone; (3) bone marrow; (4) liver; (5) spleen; (6) adrenal glands; (7) kidney; (8) lung; (9) heart; (10) urinary bladder; (11) gall bladder; (12) thyroid; (13) brain; (14) gonads; (15) gastrointestinal tract; and (16) adjacent organs of interest.

The amount of radiation delivered by internal administration of diagnostic radiopharmaceuticals should be calculated by internal radiation dosimetry. The absorbed fraction method of radiation dosimetry has been described by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and the International Commission on Radiological Protection (ICRP) (see also 21 CFR 361.1 (b)(3)(iv)).

The methodology used to assess radiation safety should be specified. The mathematical equations used to derive the radiation doses and the absorbed dose estimates should be provided along with a full description of assumptions that were made. Sample calculations and all pertinent assumptions should be listed and submitted.

Safety hazards for patients and health care workers during and after administration of the radiolabeled antibody should be identified, evaluated, and managed appropriately.

2. Calculation of Radiation Dose to the Target Organ(s) or Tissue(s)

The following items should be determined based on the average patient:

a. The amount of radioactivity that accumulates in the target tissue(s) or organ(s).

b. The amount of radioactivity that accumulates in tissues adjacent to the target tissue(s) or organ(s).

c. The residence time of the diagnostic radiopharmaceutical in the target tissue(s) or organ(s) and in adjacent regions.

d. The radiation dose from the radionuclide, including the free radionuclide and any daughter products generated by decay of the radionuclide.

e. The total radiation dose from bound, free, and daughter radionuclides associated with the diagnostic radiopharmaceutical, based upon immediate administration following preparation and upon delayed administration at the end of the allowed shelf life.

3. Maximum Absorbed Radiation Dose

The amount of radioactive material administered to human subjects should be the smallest radiation dose that is practical to perform the procedure without jeopardizing the benefits obtained.

a. The amount of radiation delivered by the internal administration of diagnostic radiopharmaceuticals should be calculated by internal radiation dosimetry using both the MIRD and ICRP methods. When making the radiation dosimetry safety assessment, the higher calculation of the two should be used.

b. Because of known or expected toxicities associated with radiation exposure, dosimetry estimates should be obtained as described above.

c. Calculations should anticipate possible changes in dosimetry that might occur in the presence of diseases in organs that are critical in metabolism or excretion of the diagnostic radiopharmaceutical. For example, renal dysfunction may cause a larger fraction of the administered dose to be cleared by the hepatobiliary system (or vice versa).

d. Possible changes in dosimetry resulting from patient-to-patient variations in antigen or receptor mass should be considered in dosimetry calculations. For example, a large tumor mass may result in a larger than expected radiation dose to a target organ from a diagnostic radiopharmaceutical that has specificity for a tumor antigen.

e. The mathematical equations used to derive the estimates of the radiation dose and the absorbed dose should be provided along with a full description of assumptions that were made. Sample calculations and all pertinent assumptions should be listed.

f. Calculations of dose estimates should be performed assuming freshly labeled material (to account for the maximum amount of radioactivity) as well as the maximum shelf life of the diagnostic radiopharmaceutical (to allow for the upper limit of radioactive decay contaminants). These calculations should (1) include the highest amount of radioactivity to be administered; (2) include the radiation exposure contributed by other diagnostic procedures such as roentgenograms or nuclear medicine scans that are part of the study; (3) be expressed as gray (Gy) per megabecquerel (MBq) or per millicurie (mCi) of radionuclide; and (4) be presented in a tabular format and include doses of individual absorbed radiation for the target tissues or organs and the organs listed above in section XI.C.1.

GLOSSARY

Note: Subjects in trials of medical imaging agents may often be classified into one of four groups depending on (1) whether disease is present (often determined with a truth standard or *gold standard*) and (2) the results of the diagnostic test of interest (positive or negative). The following table identifies the variables that will be used in the definitions.

Test Result:	**Disease:**		
	Present (+)	**Absent (-)**	
Positive (+)	**a** **true positive**	**b** **false positive**	**m1 = a + b** **total with positive test**
Negative (-)	**c** **false negative**	**d** **true negative**	**m2 = c+d** **total with negative test**
	n1 = a+c **total with disease**	**n2 = b+d** **total without disease**	**N = a+b+c+d** **total in study**

Accuracy: A measure of how faithfully the information obtained using a medical imaging agent reflects reality or *truth* as measured by a truth standard or *gold standard*. Accuracy is the proportion of cases, considering both positive and negative test results, for which the test results are correct (i.e., concordant with the truth standard or *gold standard*). Accuracy = (a+d)/N.

Likelihood ratio: A measure that can be interpreted either as (a) the relative *odds* of a diagnosis, such as being diseased or nondiseased, for a given test result, or (b) the relative *probabilities* of a given test result in subjects with and without the disease. This latter interpretation is analogous to a relative risk or risk ratio.

1. For tests with dichotomous results (e.g., positive or negative test results), the likelihood ratio of a positive test result may be expressed as LR(+), and the likelihood of a negative test result may be expressed as LR(-). See equations below.

2. For tests with several levels of results (e.g., tests with ordinal results), the likelihood ratio may be used to compare the proportions of subjects with and without the disease at each level of the test result.

$$LR(+) = \frac{\frac{a}{n1}}{\frac{b}{n2}} = \frac{sensitivity}{1 - specificity} = \frac{TruePositiveRate}{FalsePositiveRate} = \frac{\frac{a}{b}}{\frac{n1}{n2}} = \frac{PostTestOdds(+)}{PreTestOdds}$$

$$LR(-) = \frac{\frac{c}{n1}}{\frac{d}{n2}} = \frac{1 - sensitivity}{specificity} = \frac{FalseNegativeRate}{TrueNegativeRate} = \frac{\frac{c}{d}}{\frac{n1}{n2}} = \frac{PostTestOdds(-)}{PreTestOdds}$$

LR(+): *Interpreted as relative odds:* LR(+) is the post-test odds of the disease (among those with a positive test result) compared to the pretest odds of the disease.

Interpreted as relative probabilities: LR(+) is the probability of a positive test result in subjects with the disease compared to the probability of a positive test result in subjects without the disease.

LR(-): *Interpreted as relative odds:* LR(-) is the post-test odds of the disease (among those with a negative test result) compared to the pretest odds of the disease.

Interpreted as relative probabilities: LR(-) is the probability of a negative test result in subjects with the disease compared to the probability of a negative test result in subjects without the disease.

Negative predictive value: The probability that a subject does not have the disease given that the test result is negative. Synonyms include *predictive value negative*. Negative predictive value = d/m2.

Odds: The probability that an event will occur compared to the probability that the event will not occur. For dichotomous events (e.g., for test results that are either positive or negative), the odds are defined as follows: Odds = (probability of the event)/(1 - probability of the event).

Odds ratio: A measure of the amount of association between the presence or absence of disease and the diagnostic test results. Synonyms include *cross-product ratio.*

$$OddsRatio = \frac{\frac{a}{m1}}{\frac{b}{m1}} \Big/ \frac{\frac{c}{m2}}{\frac{d}{m2}} = \frac{\frac{a}{n1}}{\frac{c}{n1}} \Big/ \frac{\frac{b}{n2}}{\frac{d}{n2}} = ad/bc$$

Positive predictive value: The probability that a subject has disease given that the test result is positive. Synonyms include *predictive value positive*. Positive predictive value = a/m1.

Post-test odds of disease: The odds of disease in a subject after the diagnostic test results are known. Synonyms include *posterior odds of disease*. For subjects with a positive test result, the post-test odds of disease = a/b. For subjects with a negative test result, the post-test odds of disease = c/d. The following expression shows the general relationship between the post-test odds and the likelihood ratio: Post-test odds of disease = Pretest odds of disease x Likelihood ratio.

Post-test probability of disease: The probability of disease in a subject after the diagnostic test results are known. Synonyms include *posterior probability of disease*. For subjects with a positive test result, the post-test probability of disease = a/m1. For subjects with a negative test result, the post-test probability of disease = c/m2.

Precision: A measure of the reproducibility of a test, including reproducibility within and across drug doses, rates of administration, routes of administration, timings of imaging after drug administration, instruments, instrument operators, patients, and image interpreters, and possibly other variables. Precision is usually expressed in terms of variability, using such measures as confidence intervals and/or standard deviations. Precise tests have relatively narrow confidence intervals (or relatively small standard deviations).

Pretest odds of disease: The odds of disease in a subject before doing a diagnostic test. Synonyms include *prior odds of disease.* Pretest odds of disease = n1/n2.

Pretest probability of disease: The probability of disease in a subject before doing a diagnostic test. Synonyms include *prevalence of disease* and *prior probability of disease*. Pretest probability of disease = n1/N.

Probability: The likelihood of occurrence of an event, expressed as a number between 0 and 1 (inclusive).

Sensitivity: The probability that a test result is positive given the subject has the disease. Synonyms include *true positive rate*. Sensitivity = a/n1.

Specificity: The probability that a test result is negative given that the subject does not have the disease. Synonyms include *true negative rate*. Specificity = d/n2.

Truth standard (gold standard): An independent method of measuring the same variable being measured by the investigational drug that is known or believed to give the *true* value of the measurement.